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Comments from Academics, Scientists and Clinicians on the Risk Evaluation Scoping Efforts Under TSCA for Ten Chemical Substances

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These comments are submitted on behalf of the undersigned academic, scientists, and clinicians. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical under consideration in these risk evaluations. The co-signers' institutional affiliations are included for identification purposes only and do not necessarily imply any institutional endorsement or support, unless indicated otherwise.

We appreciate the opportunity to provide written comments on the scope of risk evaluations for the first ten chemicals substances for risk evaluations pursuant to the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety of the 21st Century Act (Lautenberg TSCA). Collectively, these chemicals represent an aggregate production volume of more than 1 billion pounds a year in 2015.[1] Some of these chemicals have assessments, and in some cases even restrictions, under other federal programs--but none of these other programs has the mandate given to EPA under the new TSCA: to comprehensively evaluate chemicals and ensure that they do not pose an unreasonable risk to human health and the environment, with special consideration to those most vulnerable amongst us. Therefore, the task ahead for EPA is critical.

These first ten evaluations are also consequential because they will be precedent setting for the implementation of evaluation of science under TSCA. The consequent health impacts of EPA's decisions – for better or worse – will be borne by generations of American children, workers, families, and communities. With so much at stake, we welcome EPA's engagement with the public in this process and we offer EPA concrete approaches to embed the most current scientific principles in its methods to assess the hazards and risks of environmental chemicals.

Our comments address the following main points:

1. **EPA should improve its literature search and systematic review strategies to strengthen its evaluations and increase transparency.**
2. **EPA needs to consider aggregate exposure within and across populations; otherwise it will underestimate risk. Aggregate exposure should include legacy uses, uses where a chemical is present as a contaminant or by-product, and uses already assessed by EPA.**
3. **EPA appropriately identifies factors to consider to identify populations subject to greater exposures. EPA should also address susceptible sub-populations, following recommendations**

[1] This is the aggregate production volume estimate for the 8 chemicals with production volume information available. For asbestos and pigment violet 29, manufacturers/ importers claimed production volumes as confidential business information (CBI).

from the National Academies of Sciences (NAS) to identify susceptible sub-populations based on established extrinsic and intrinsic factors that increase vulnerability.

4. **EPA should rely on existing IRIS assessments for hazard identification. Moving forward, EPA should complete hazard identification or add additional studies only through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report.**
5. **For risk characterization, EPA should use defaults and methods that account for the full range of risks in the population and that will form the basis of decisions that protect the public's health.**
6. **Confidential Business Information (CBI) claims should not be used to obscure critical data and information from the public.**

We are appreciative of the opportunity to provide public input and we look forward to continuing to participate in such opportunities in the near future. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

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DETAILED COMMENTS

1. **EPA should improve its literature search and systematic review strategies to strengthen its evaluations and increase transparency.**

Overall, we strongly commend the EPA for its efforts to utilize a systematic and transparent method of research synthesis to reach a concise, strength of evidence conclusion about the human health hazard resulting from exposures to these ten chemicals. Efforts to integrate systematic review methods, including the explicit development of search terms, strategies, and inclusion/exclusion criteria beforehand, is relatively new in EPA's chemical assessment and as such, we applaud the EPA for this and its general improvements in its hazard assessment methodology. These scoping documents generally provide an important infrastructure for outlining EPA's screening approach for identifying relevant references and to document decisions made in the process of identifying the body of scientific literature that will be evaluated in the chemical assessments.

To improve on this document and advance EPA's uptake of systematic review methods of research synthesis, we identify the following opportunities for improvement:

EPA should not exclude studies based on language. EPA's search strategy is limited to English-only studies. The exclusive reliance on English-language studies may not represent the entire body of

available evidence, and studies have suggested that language bias might lead to erroneous conclusions.[2] Furthermore, when considering the inclusion or update of an existing systematic review, studies have found that language-inclusive systematic reviews (including studies in languages other than English) were of the highest quality, compared with other types of reviews.[3] Online translation tools are readily available to allow screeners to quickly evaluate study abstracts for relevance, and therefore we recommend EPA to incorporate non-English language studies in their screening and not simply exclude these potentially relevant papers.

EPA should provide exclusion reasons for off topic citations. In the Bibliography Supplemental File for the Scope Documents, EPA has provided lists of bibliographic citations that were identified and screened from the initial literature search and the initial categorization of whether citations were *on topic* or *off topic.* We recommend EPA additionally provide exclusion reasons that were used to come to the conclusion that each citation was *off topic*, as this is a standard recommendation to fulfill transparency in documenting and reporting all decisions made in the study selection process.[4] This is particularly important as EPA has proposed to do its screening in Distiller, a proprietary software that presumably will not be made publicly available, raising concerns regarding the transparency and reproducibility of this screening step.

EPA should consider other tools for systematic review. EPA has also proposed to extract data results in the DRAGON software. We strongly encourage EPA to also consider other potential software tools that have been developed and actively incorporated into the process of systematic review, such as Swift Reviewer,[5] Active Screener,[6] HAWC (Health Assessment Workplace Collaborative).[7] These tools will help to ensure consistent and transparent execution and presentation of reviews and increase transparency of EPA assessment. Furthermore, we urge EPA to work with the National Toxicology Program and other organizations involved in these efforts in an ongoing basis to develop these and other open source tools to train scientists in their use. We believe that such infrastructure development will be critical to increasing the efficiency of chemical assessments and to expedite uptake of systematic reviews in environmental health.

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[2] Morrison, A., Polisena, J., Husereau, D., Moulton, K., Clark, M., Fiander, M., Mierzwinski-Urban, M., Clifford, T., Hutton, B. and Rabb, D., 2012. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *International journal of technology assessment in health care*, *28*(2), pp.138-144.

[3] Moher, D., Pham, B., Lawson, M.L. and Klassen, T.P., 2003. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. *Health Technol Assess*, *7*(41), pp.1-90.

[4] McDonagh M et a. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality. 2008.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J. and Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine*, *6*(7), p.e1000100.

Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. March 2011. Available from: http://handbook-5-1.cochrane.org/chapter_7/7_2_5_selecting_excluded_studies.htm

[5] Howard, B.E., Phillips, J., Miller, K., Tandon, A., Mav, D., Shah, M.R., Holmgren, S., Pelch, K.E., Walker, V., Rooney, A.A. and Macleod, M., 2016. SWIFT-Review: a text-mining workbench for systematic review. *Systematic reviews*, *5*(1), p.87.

[6] https://www.sciome.com/swift-activescreener/

[7] [HYPERLINK "https://hawcproject.org/about/"]

EPA should have two independent reviewers for screening steps. EPA has outlined its process for screening title and abstracts of papers as having a single reviewer reviewing papers to determine whether the study is *on-topic* or *off-topic*. As part of this process, a senior-level technical expert in the topic area of interest reviewed the appropriateness of the assigned tags for "the first batch of studies" and provided feedback to the screener. Senior-level technicians also provided feedback and guidance on specific references to the individual screeners as needed during the screening and tagging process. From the description of this process, it does not appear that two independent reviewers screen all titles and abstracts for potential inclusion. Using two independent reviewers is a standard approach in systematic reviews and therefore we strongly recommend that EPA include a second independent reviewer within this process to ensure that **all** studies are screened by two reviewers at each step (title and abstract and full text).

EPA should clearly document decisions related to the identification and search. For example, it was unclear how many studies were included in the first batch of studies reviewed by the senior-level technician—these decisions should be clearly specified beforehand as to the number (or percent) that will be reviewed by this independent reviewer. Furthermore, it is unclear how many studies the senior-level technical experts are reviewing generally as to their additional feedback and guidance to individual screeners. This should be more clearly stated and described beforehand in these protocols.
We recommend EPA broaden the set of studies that are initially screened in the first batch to ensure consistency across reviewers and demonstrated understanding of protocol instructions by all reviewers before moving on to screening the remaining records. It is stated in the Gray Literature Search Results that individual screeners would screen and tag 10 references that would be then independently reviewed by the senior-level technical expert. However, this does not seem to be an adequate number of studies as it is a small number relative to the expected number of records that will ultimately be screened.

EPA should clarify how it will handle discrepancies in the inclusion/exclusion and tagging process. As it is stated in its current protocol, it appears that the senior-level technical expert has the final say in determining the final inclusion/exclusion decision and tagging, for the subset of studies they evaluate. However, this should be clarified and we also highly recommend that a third party reviewer be incorporated as an arbiter for these decisions if consensus cannot be reached between the two reviewers, as is typically standard in systematic reviews.

EPA should stratify its exclusion criteria separately at the title and abstract and full-text screening steps. It is likely that title and abstracts of papers would not contain sufficient detail to evaluate all exclusion criteria—many of these would likely only be identified in the full-text of the paper. To increase the efficiency of the screening process, it would help to create a subset of exclusion criteria most relevant when screening the title and abstracts of records versus the larger set of exclusion criteria relevant to screening the full text of records.

EPA should clearly outline the process for handling anticipated overlap with literature relevant to multiple topics. EPA should describe how this will be addressed by the screeners and whether the same reviewer will be responsible for screening papers with inclusion/exclusion criteria across multiple topics or whether different reviewers are responsible only for screening studies for one particular topic. Additional details in regards to the process by which this screening will occur would be helpful. Given the breadth of each assessment (searching literature related to fate, engineering, exposure, human health, and environmental hazard) and the complexity of the screening process (tagging *on-topic* and *off-topic* literature and using additional sub-categories or sub-tags to allow for additional

categorization), there appears to be the potential for individual papers to fall into different topic categories and have many different tags and sub-tags applied to indicate their relevance. However, it is unclear how this will be organized in the screening phase. Search strategies and inclusion/exclusion criteria appear to have been developed specifically for each literature topic and the potential overlap of literature relevant to multiple topics is not addressed.

EPA should explicitly include stopping rules for when the list of relevant studies will be considered final. There is no discussion of stopping dates or the process of updating the literature search to search for newer studies. Newer scientific studies will inevitably continue to appear in scientific journals and it will be impossible to continually attempt to include all these studies in a chemical assessment. To meet the deadlines as mandated by the Lautenberg Amendments, EPA should state clear stopping rules in the form of deadlines or criteria for when the body of included relevant studies will be finalized for the purposes of the chemicals assessment.

EPA should ensure gray literature search results are adequately screened. EPA's gray literature search strategy proposes to utilize Google's API to develop custom searches and return the first 100 results, sorted by predicted relevancy so that the results likely to be most relevant are screened first. It is unclear why this number is limited to only the first 100 and whether there was an empirical reason for why this particular number was selected. We recommend that EPA ensure that an adequate number of search results are screened, in particular considering that the gray literature can contribute potentially important information relevant to toxicity, mode of action, exposure, fate and transport, engineering or occupational exposure, or existence of publication bias.

EPA should consider "snowball searching," where the citations of included (i.e., *on-topic*) references are searched as well as using databases such as Web of Science to search for references that cite the included citations. EPA states that it plans on assessing the specificity and efficiency of the literature searches, through comparison of references either cited in existing problem formulation and risk assessment documents, in the public use documents and supporting life cycle diagrams, and comparison of the references cited in review articles. Snowball searching will contribute to the evaluation of the specificity and efficiency of its literature searches, and also help to identify newer relevant studies that could potentially be included that have not yet been indexed in main databases such as PubMed.

EPA should incorporate appropriate tools for updating and evaluating systematic reviews in their chemical assessments. Garner et al., as part of efforts by a Cochrane Collaboration panel for updating guidance for systematic reviews, published guidance in 2016 for determining when it is appropriate to update a systematic review and outlining the steps for performing the update.[8] We have attached this guidance as an Appendix to these comments. EPA should evaluate the Cochrane tool's applicability to environmental chemicals given that Cochrane systematic reviews are geared towards reviews of clinical intervention evidence, so these tools may require updating and tailoring for an application to environmental health data.

[8] Garner P, Hopewell S, Chandler J, MacLehose H, Akl EA, Beyene J, Chang S, Churchill R, Dearness K, Guyatt G, Lefebvre C. When and how to update systematic reviews: consensus and checklist. bmj. 2016 Jul 20;354:i3507.

A recent NAS report[9] recommends EPA should develop policies and procedures to allow the agency to identify, use and update existing systematic reviews. The committee also noted that it was important that the existing systematic review's study question directly addresses EPA's topic of interest and that the methods are critically evaluated before the systematic review is used and updated. EPA should ensure that only the highest quality systematic reviews be considered appropriate for use. It will be critical for EPA to develop tools to assist with the process of evaluating existing systematic reviews, particularly as this field continues to rapidly expand and more systematic reviews relevant to environmental health questions are published in the scientific literature, potentially of variable quality.

One tool which might be helpful for evaluating the risk of bias in systematic reviews is the ROBIS tool, which the NAS committee utilized in their report.[10] This tool was developed using rigorous methodology and can be applied for evaluating internal validity of systematic reviews in conjunction with other available tools to critically appraise and assess their quality. Of particular note is the strong emphasis on the recommendation that tools such as ROBIS should not be used to generate a composite quality score, as it has been well-documented that scoring can lead to bias in evaluation of the studies.[11] As such, the ROBIS tool presents several options for visually and graphically presenting results from risk of bias assessments based on individual domains or the overall rating, enabling reviewers to highlight particular areas of concern or reviews that are most relevant to the target question of interest.

Another tool which may be helpful in this process is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), used by authors of systematic reviews to improve the reporting of elements relevant to the systematic review and meta-analyses.[12] Increasingly, scientific journals are requiring the inclusion of checklists such as PRISMA with the submission of systematic reviews considered for publication. Although this tool is used to evaluate study reporting, and is not an assessment instrument to gauge the quality of a systematic review, it can still provide a useful framework to identify reported components of an existing systematic review in the process of evaluating quality or to identify missing components requiring follow-up with study authors to obtain additional information.

Furthermore, we strongly encourage EPA to evaluate the potential for financial conflicts of interest as an element in their study design. This is currently included as a consideration in evaluation risks of bias in some frameworks, such as the Navigation Guide,[13] and extracted for consideration as an additional

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[9] The National Academies of Sciences. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, D.C.: National Academies Press; 2017.

[10] Id.

[11] Jüni, P., Witschi, A., Bloch, R. and Egger, M., 1999. The hazards of scoring the quality of clinical trials for meta-analysis. *Jama*, *282*(11), pp.1054-1060.

Whiting, P., Harbord, R. and Kleijnen, J., 2005. No role for quality scores in systematic reviews of diagnostic accuracy studies. *BMC Medical Research Methodology*, *5*(1), p.19.

Whiting, P., Savović, J., Higgins, J.P., Caldwell, D.M., Reeves, B.C., Shea, B., Davies, P., Kleijnen, J. and Churchill, R., 2016. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *Journal of clinical epidemiology*, *69*, pp.225-234.

[12] [HYPERLINK "http://www.prisma-statement.org/"]; Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015 Jan 1;4(1):1.

[13] Woodruff, T.J. and Sutton, P., 2011. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. *Health affairs*, *30*(5), pp.931-937.

domain in other frameworks, such as that developed by the National Toxicology Program's (NTP) Office of Health Assessment and Translation (OHAT).[14] The Cochrane Collaboration's risk of bias tool does not currently include a specific domain for bias related to study funding source, but this is an area of active discussion among its members.[15] The Cochrane Collaboration has recognized the importance of identifying study funding source, which has been empirically shown to be associated with biases.[16] A recent report from the NRC recommended that the U.S. EPA consider funding sources in their risk of bias assessment conducted for systematic reviews.[17]

We also strongly recommend EPA identify tools that may potentially not be appropriate for human health chemical assessments. Many tools are currently being developed for evaluating risk of bias, quality, and strength of evidence for individual studies as well as for systematic reviews. It is critical that EPA evaluate tools developed in other fields that may be relevant, such as for clinical or preclinical animal or human studies, as these tools could potentially be modified for an application to questions of environmental health relevance. However, these tools should be applied with caution—due to the differences in the types of evidence under evaluation a direct application to a difference evidence base than intended could lead to biased and erroneous conclusions.[18]

2. EPA needs to consider aggregate exposure within and across populations; otherwise it will underestimate risk. Aggregate exposure should include legacy uses, uses where a chemical is present as a contaminant or by-product, and uses already assessed by EPA.

In general, EPA is proposing to consider three populations for exposure assessment: 1) Occupational users and non-users; 2) consumers and bystanders; and 3) general population. We strongly recommend that EPA calculate the aggregate exposures within and across these populations-- risk will be underestimated if it does not include these real-world exposures. Exposures within a population should also be aggregated (rather than considered in isolation) in order to estimate the general population's actual exposure to the chemical—for example, through exposures from food, water and air.

Woodruff, T.J. and Sutton, P., 2014. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environmental health perspectives*, *122*(10), p.1007.

[14] NTP OHAT Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration [HYPERLINK "https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf"]

[15] Bero LA. Why the Cochrane risk of bias tool should include funding source as a standard item. *Cochrane Database Syst Rev. 2013 Dec 20; (12):ED000075.*

Sterne JA. Why the Cochrane risk of bias tool should not include funding source as a standard item. *Cochrane Database Syst Rev. 2013 Dec 20; (12):ED000076.*

[16] Krauth D, Anglemyer A, Philipps R, Bero L. Nonindustry-sponsored preclinical studies on statins yield greater efficacy estimates than industry-sponsored studies: a meta-analysis. *PLoS Biol. 2014 Jan; 12(1):e1001770*

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev. 2012 Dec 12; 12():MR000033.*

[17] NRC (National Research Council). Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC:National Academies Press. 2014.

[18] Nachman, K.E., Lam, J., Schinasi, L.H., Smith, T.C., Feingold, B.J. and Casey, J.A., 2017. O'Connor et al. systematic review regarding animal feeding operations and public health: critical flaws may compromise conclusions. *Systematic Reviews*, *6*(1), p.179.

Further, as shown in the Figure below, exposures must also be aggregated across populations. Consumers and workers are part of the general population—that is, since workers and consumers also eat food and drink water, they will have the same exposures as the general population, in addition to the anticipated exposures on-the-job or from consumer products. Some workers will also be consumer product users, so they have the potential to face general, consumer product, and on-the-job exposures. These specific exposure scenarios must be accounted for in EPA's exposure estimation to ensure that such individual exposures are adequately considered and integrated into the risk assessment.

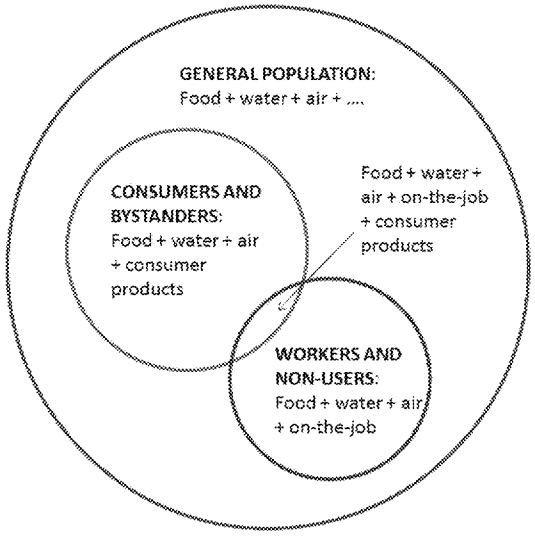

Figure: EPA must assess aggregate exposures within and across all the populations for accurate exposure assessment.

In the Introduction section of the chemical Scope documents, EPA states that it "may consider background exposures from legacy use, associated disposal, and legacy disposal as part of an assessment of aggregate exposure or as a tool to evaluate the risk of exposures resulting from non-legacy uses."[19] This falls short of the analysis required under Lautenberg TSCA. It is critical that EPA consider ongoing exposures from legacy uses and disposal, and includes these as part of the aggregate exposure assessment. Asbestos and HBCD are two examples of this, as they have enormous volumes in place in buildings and existing infrastructure. The Healthy Building Network estimates there are 66 million- 132 million pounds (30,000-60,000 metric tons) of HBCD in insulation in existing buildings[20] — these reservoirs in-place are and will continue to be critical sources of ongoing exposures. HBCD was also used in cars and furniture, which are long-lived consumer items that will continue to contribute to ongoing exposures for years to come.

Another example is 1,4-dioxane, which was historically used as a chemical stabilizer for chlorinated solvents. Many groundwater aquifers are contaminated with 1,4-dioxane, and the extent of legacy

[19] See, for example, US EPA (2017). Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster. Pg. 12

[20] Safer Chemicals, Healthy Families et al. Comments to the U.S. Environmental Protection Agency (EPA) on the Scope of its Risk Evaluation for the TSCA Work Plan Chemicals: CYCLIC ALIPHATIC BROMIDE CLUSTER or HEXABROMOCYCLODODECANE (HBCD). March 15, 2017. [HYPERLINK "https://healthybuilding.net/uploads/files/saferchemicals-hbcd.pdf" \h]

contamination of groundwater is likely underestimated.[21] Also, 1,4-dioxane occurs in a wide variety of products including personal care products, detergents, waxes, and antifreeze, and 1,4-dioxane is a by-product in manufacturing processes involving ethylene oxide, such as the production of polyethylene terephthalate (PET), polyester, and surfactants. The use and disposal of 1,4-dioxane has led to past environmental contamination which contributes to on-going exposures.[22] The physical and chemical properties of 1,4-dioxane render it a persistent and highly mobile water contaminant: it is highly miscible in water.[23] Exposures via drinking water are documented back to the 1980s and continue today.[24] Results from EPA's Third Unregulated Contaminant Monitoring Rule (UCMR3) highlight that over 13% of 4,905 public drinking water systems serving >10,000 people had concentrations of 1,4-dioxane above the EPA Reference Concentration of 0.35 ppb 1,4-dioxane.[25] Furthermore, the UCMR3 results do not capture exposures in communities served by small public drinking water systems serving <10,000 people.[26] Approximately 27% of the US population is served by small public drinking water systems.[27] Thus, it will be critical for EPA to consider the population's current exposure to 1,4-dioxane via sources like drinking water as part of their assessment for health risks.

When a chemical is present in products or media as a contaminant/ by-product, EPA needs to include and assess these exposures. We strongly recommend against ignoring or discounting these potential exposures routes. For example, EPA proposes to exclude from consideration conditions of use of 1,4-dioxane when it is present as contaminant in a wide variety of items, including household detergents, cosmetics/ toiletries, and foods.[28] This exclusion is not scientifically justified. Cosmetics and personal care products have the potential to contribute significantly to exposures, since people are applying them directly to their bodies, often multiple times per day, every day.

Finally, in the exposure assessments for methylene chloride, N-methylpyrrolidone and trichloroethylene, EPA is proposing to exclude uses it already assessed.[29] We agree that EPA does not need to re-assess these uses; these evaluations have been completed and finalized. However, unless and until such uses

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[21] David T. Adamson, Shaily Mahendra, Kenneth L. Walker, Jr., Sharon R. Rauch, Shayak Sengupta, and Charles J. Newell. A Multisite Survey To Identify the Scale of the 1,4-Dioxane Problem at Contaminated Groundwater Sites. *Environmental Science & Technology Letters* 2014 1 (5), 254-258 DOI: 10.1021/ez500092u

[22] Agency for Toxic Substances and Disease Registry. TOXICOLOGICAL PROFILE FOR 1,4-DIOXANE. Atlanta, GA; 2012.

[23] U.S. Environmental Protection Agency. Integrated Risk Information System (IRIS). 1,4-Dioxane (CASRN 123-91-1). Washington, D.C.; 2013. [HYPERLINK "http://www.epa.gov/iris/subst/0326.htm"].

[24] Dietrich, A.M., D.S. Millington, and R.F. Christman. 1983. Specific identification of organic pollutants in Haw River water using gas chromatography/mass spectrometry. WRRI Report No. 206. North Carolina State University, Raleigh, NC.

[25] U.S. Environmental Protection Agency. Integrated Risk Information System (IRIS). 1,4-Dioxane (CASRN 123-91-1). Washington, D.C.; 2013. [HYPERLINK "http://www.epa.gov/iris/subst/0326.htm"].

U.S. Environmental Protection Agency. Unregulated Contaminant Monitoring Rule 74 FR 51850, EPA-HQ-OW-2007-1189 FRL-8963-6. Washington, D.C.; 2009. [HYPERLINK "https://federalregister.gov/a/E9-24287"].s

[26] Knappe, D.R.U., Lopez-Velandia, C., Hopkins, Z., & Sun, M. (2016). Occurrence of 1,4-Dioxane in the Cape Fear River Watershed and Effectiveness of Water Treatment Options for 1,4-Dioxane Control. NC Water Resources Research Institute.

[27] EPA. 2017. Small Drinking Water Systems Research https://www.epa.gov/water-research/small-drinking-water-systems-research-0 (accessed September 17, 2017).

[28] US EPA (2017). Scope of the Risk Evaluation for 1,4-dioxane. Pg. 21

[29] US EPA (2017). Scope of the Risk Evaluation for Methylene Chloride (Dichloromethane, DCM). Pg. 30
US EPA (2017). Scope of the Risk Evaluation for N-Methylpyrrolidone. Pg. 19-20
US EPA (2017). Scope of the Risk Evaluation for Trichloroethylene. Pg. 27

are banned, the exposures from these uses continue. Therefore, the new risk evaluations need to consider the contributions of these uses to exposures by using the exposure values from the previous assessments.

For the occupational exposure analysis plan, EPA states it will "Consider and incorporate applicable engineering controls and/or personal protective equipment into exposure scenarios."[30] However, these are not realistic assumptions nor are they appropriate for public health protection. EPA's own research shows that the primary factors influencing whether a user understands label information are the users' literacy and numeracy, which frequently correlate with the users' education and income.[31] Therefore, people with less education, lower income, and less advanced literary skills will be the most likely to not understand label instructions. These individuals already disproportionately bear the burden of exposures to multiple environmental hazards and the resulting health impacts; thereby placing further burden on this already stressed susceptible subpopulation. Further, appropriate personal protective equipment (PPE) for workers is often not provided by employers, or may not be fitted or working properly. When evaluating occupational exposures, EPA needs to take into consideration all potential and feasible routes of exposure, and should not exclude exposure routes based on assumptions of PPE and/ or exposure controls in place. These controls are not guaranteed and may change in the future, so to assume zero exposure via these routes would be inappropriate and a failure to adequately ensure health protections, especially for susceptible sub-populations as required by the Lautenberg TSCA.

In summary, EPA needs to account for all the sources of exposure or it will underestimate risk for all 10 chemicals. When analyzing aggregate exposures, "sentinel exposure" may be considered simultaneously, where appropriate. However, these are not mutually exclusive and EPA should not incorporate sentinel to the exclusion of aggregate.

3. **EPA appropriately identifies factors to consider to identify populations subject to greater exposures. EPA should also address susceptible sub-populations, following recommendations from the National Academies of Sciences (NAS) to identify susceptible sub-populations based on established extrinsic and intrinsic factors that increase vulnerability.**

In general, EPA proposes to consider workers and occupational non-users, consumer and by-standers, and other groups within the general population in proximity to conditions of use as sub-populations who experience greater exposures. In particular, EPA has appropriately identified people who live or work near manufacturing, processing, distribution, use or disposal sites as facing greater exposures. Such communities are often low income and/ or people of color, exposed to a disproportionate share of pollution, environmental hazards, social and economic stressors. Multiple exposures to chemical and non-chemical stressors collectively increase the risk of harm, combined with synergistic effects with other health stressors in their daily lives such as limited access to quality health care.[32,33]

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[30] See, for example, US EPA (2017). Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster. Pg. 45

[31] US Environmental Protection Agency (EPA). 2016. "The Effectiveness of Labeling on Hazardous Chemicals and Other Products." Office of Chemical Safety and Pollution Prevention. RIN 2079-AK07.

[32] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.

[33] Vesterinen HM, Morello-Frosch R, Sen S, Zeise L, Woodruff TJ. Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. Meliker J, editor. PLoS One. 2017 Jul 12;12(7):e0176331.

EPA's risk evaluation needs to fully account for the reality of cumulative exposures, as recommended by the NAS in their Phthalates and Cumulative Risk report.[34] As described below, EPA can use "default values" to account for cumulative exposures.

In regards to greater susceptibility, EPA's considerations for addressing susceptibility vary considerably across the 10 chemicals. EPA should apply a consistent approach to addressing susceptibility across the 10 chemicals. The following are well-known factors that increase biologic sensitivity or reduce resilience to exposures,[35,36] and these as well as other relevant factors should be standard considerations for all 10 chemicals to identify susceptible sub-populations:

Intrinsic/ endogenous factors

- Genetic polymorphisms/ genetics/ genetic makeup
- Health status/ nutritional status/ disease status/ pre-existing conditions
- Prenatal lifestage
- Age

Extrinsic factors

- Multiple exposures/ co-exposures
- Race/ ethnicity
- Socioeconomic status (SES)

For example, the prenatal lifestage is the most sensitive to developmental and reproductive toxicants, and women of child-bearing age should be considered as a susceptible sub-population for any chemicals with such hazards. Women of reproductive age are not specifically identified as a potential susceptible sub-population for pigment violet 29, TCE, NMP, PERC, or HBCD, even though EPA will consider reproductive and developmental toxicity hazards for these chemicals.

As discussed below, science-based defaults should be used to account for these and other susceptibilities, unless there is there is chemical-specific data available to support increasing or decreasing the default.

4. EPA should rely on existing IRIS assessments for hazard identification. Moving forward, EPA should complete hazard identification or add additional studies only through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report.

EPA cites existing IRIS assessments for five chemicals; because these are EPA's own assessments which have gone through the Agency's peer-review process, and in some cases NAS review, EPA can rely on these existing finalized, authoritative assessments for hazard identification.

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[34] National Research Council. Committee on the Health Risks of Phthalates, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies. 2008. Phthalates and cumulative risk assessment: the task ahead. Washington, D.C.: National Academies Press.

[35] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.

[36] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009.

Moving forward, a weight of evidence evaluation is required by law, which EPA defines as:

> "Weight of scientific evidence means a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance."[37]

Therefore, EPA should use a systematic review process for evaluating scientific information for chemicals that do not have an IRIS assessment and for any additional studies that will be considered for the chemicals that have IRIS assessments.

For the scoping document, EPA should include all hazards identified in the literature, and not make decisions about their relevance to the risk evaluation until a systematic review has been completed. For a number of chemicals, EPA has inappropriately drawn conclusions about hazards prior to the completion of a systematic review. Some examples are given in the table below where EPA concludes that HBCD, NMP and pigment violet 29 are not genotoxic based on previous assessments and without conducting a systematic review.

Chemical	Example Text from EPA Scoping Document
HBCD	"Available data suggest that HBCD is not genotoxic. Existing assessments have also concluded, based on genotoxicity information and a limited lifetime study, that HBCD is not carcinogenic (NICNAS, 2012; EINECS, 2008; TemaNord, 2008; OECD, 2007). Unless new information indicates otherwise, EPA does not expect to conduct additional in-depth analysis of genotoxicity or cancer hazards in the risk evaluation of HBCD at this time."[38]
NMP	"NMP is not mutagenic, based on results from bacterial and mammalian *in vitro* tests and *in vivo* systems and is not considered to be carcinogenic (RIVM, 2013; OECD, 2007; WHO, 2001). Unless new information indicates otherwise, EPA does not expect to conduct additional in-depth analysis of genotoxicity and cancer hazards in the NMP risk evaluation."[39]
Pigment violet 29	"Testing for carcinogenicity of Pigment Violet 29 has not been conducted. However, negative genotoxicity results, structure-activity considerations and the expectation of negligible absorption and uptake of Pigment Violet 29 (based on very low solubility), indicate carcinogenicity of Pigment Violet 29 is unlikely. Unless new information indicates otherwise, EPA does not expect to conduct additional, in-depth analyses of genotoxicity and cancer hazards in the risk evaluation of Pigment Violet 29."[40]

The National Academies recently released a report with recommendations on implementation of systematic review for EPA's chemical evaluations (which we will refer to as the 'NAS Systematic Review

[37] 82 Fed. Reg. 138, 33748
[38] US EPA (2017). Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster. Pg.36
[39] US EPA (2017). Scope of the Risk Evaluation for N-Methylpyrrolidone. Pg. 36
[40] US EPA (2017). Scope of the Risk Evaluation for Pigment Violet 29. Pg.29

report' for simplicity).[41] First, they recommend that EPA should develop policies and procedures that allow the agency to use and update existing systematic reviews, since the committee concluded that could potentially save time and resources. EPA should conduct a review to determine whether there are existing systematic reviews on the topic of interest and if there is, EPA should evaluate it to determine if it is high-quality. The NAS recommends that EPA should build on existing high-quality reviews to incorporate new studies and use the updated systematic review as a basis for its assessment. The assessments cited by EPA to support the hazard identification claims are not systematic reviews; even if they were, EPA should evaluate them for quality before relying on their conclusions.

Second, it is very likely that additional studies have been published since the assessments EPA cites were completed. EPA should develop criteria to evaluate the internal validity (risk of bias) of individual studies, utilizing existing tools that have been developed and empirically demonstrated on environmental health studies such as the Navigation Guide or the OHAT approach.[42] We also recommend that EPA not using a scoring system to evaluate study quality. Specifically, we note that empirically validated approaches in the clinical sciences such as Cochrane discourage using a numerical scale scoring approach for evaluating study quality because calculating a score requires choosing a weighting scheme for each component, which generally is nearly impossible to justify.[43] Furthermore, a study might be well designed to eliminate bias, but because the study failed to report details in the publication under review, it will receive a low score--most available scoring systems include a mix of risk of bias and reporting biases which is inappropriate. Additionally, quality scores have been shown to be invalid for assessing risk of bias in clinical research.[44] The current standard in evaluation of both clinical and environmental health research calls for reporting each component of the assessment tool separately and not calculating an overall numeric score.[45]

Data generated by alternative test methods (such as high-throughput screening methods) are not different than any other type of *in vitro* or cell-based assay data that would be considered in a systematic review. These kinds of assays provide mechanistic data, and the NAS Systematic Review report explicitly considered how mechanistic data could be utilized in a systematic review for evidence

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[41] The National Academies of Sciences. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, D.C.: National Academies Press; 2017.

[42] Woodruff, T.J. and Sutton, P., 2011. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. *Health affairs*, *30*(5), pp.931-937.

Woodruff, T.J. and Sutton, P., 2014. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environmental health perspectives*, *122*(10), p.1007.

NTP OHAT Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration [HYPERLINK "https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf"]

[43] Juni, P., A. Witschi, R. Bloch, and M. Egger. 1999. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 282(11):1054-1060.

[44] Id.

[45] Higgins, J.P.T., and S. Green, eds. 2008. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons.

Whiting, P., Harbord, R. and Kleijnen, J., 2005. No role for quality scores in systematic reviews of diagnostic accuracy studies. *BMC Medical Research Methodology*, *5*(1), p.19.

Whiting, P., Savović, J., Higgins, J.P., Caldwell, D.M., Reeves, B.C., Shea, B., Davies, P., Kleijnen, J. and Churchill, R., 2016. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *Journal of clinical epidemiology*, *69*, pp.225-234.

integration. The committee came to two conclusions. First, the same protocol for evaluating relevance and study quality must be used with mechanistic data as for any other study. For example, in the report's case study on phthalates, the committee was not able to integrate results from high-throughput assays because the cell lines used were of unknown relevance to the *in vivo* mechanism of phthalate toxicity.[46] Second, the foundation of the hazard classification in a systematic review is the animal and human data, with the mechanistic data playing a supporting role. If mechanistic data is relevant, it can be used to upgrade a hazard classification, or increase the confidence of a finding made based on evaluation of animal and human data. A hazard classification is never made based on high-throughput or other kinds of mechanistic data alone.[47]

5. For risk characterization, EPA should use defaults and methods that account for the full range of risks in the population and that will form the basis of decisions that protect the public's health.

Defaults

We strongly support the use of health protective defaults to incorporate factors that reflect the range of variability and susceptibility in the population to ensure risks are not underestimated. The importance of using protective science-based defaults was highlighted by the NAS in 2009.[48] The default should be used for factors that are known to influence risk unless there is chemical-specific data that support increasing or decreasing it; when there is inadequate information to quantitatively assess inter- or intra-species differences for a specific chemical, the defaults should be used. For example, EPA's defaults should include:

- Intra-human variability, general
- Intra-human susceptibility to carcinogens, adult
- Intra-human susceptibility to carcinogens, early life (including prenatal)
- Intra-human susceptibility to non-carcinogens, early life (including prenatal)
- Animal findings are relevant to humans
- Findings from one route of exposure are considered representative unless data show otherwise

EPA has relied on standard default values ("uncertainty" or "safety" factors) that have been applied across the board to various chemicals and health outcomes. But newer science demonstrates that EPA's typical safety factor of 10 is insufficient to account for variability due to life stage, genetics, underlying disease status, and external stressors that may be due to poverty or other difficult life conditions.

For cancer, the NAS recommended that EPA include a factor to account for human variability in response to carcinogens, as EPA's current approach inaccurately assumes that there is no variability in response. They found that a factor of 25- to 50- may account for the variability between the median individual and those with more extreme responses, and recommended 25 as a reasonable default value.[49]

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[46] The National Academies of Sciences. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, D.C.: National Academies Press; 2017. Pg. 78

[47] Id. Pp. 158-9

[48] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. Ch 4-6

[49] Id. Pg. 168

Similarly, EPA should increase or add factors that address cancer and non-cancer susceptibility during early life stages. While EPA does account for increased susceptibility to genotoxicants, it does not include the prenatal period or chemicals that can influence cancer through other mechanisms. California EPA's guidance incorporates factors to account for increased susceptibility for exposures that occur prenatally for carcinogens, non-mutagenic carcinogenic agents and non-carcinogens. Their literature review on differential susceptibility to carcinogens and non-carcinogens based on age and life stage derived age adjustment values for carcinogens which include the prenatal period[50] and increased the default intraspecies uncertainty factors for non-carcinogens to 30 and 100 for specific endpoints such as asthma or neurotoxicity. [51] At a minimum, EPA should use Cal EPA's age adjustment values and intraspecies uncertainty factors for incorporating age/early life susceptibility.

In general, developmental life stages, including the fetus, infancy, and childhood, are more vulnerable to chemical exposure and toxicity. However, typical EPA age-dependent adjustment factors account for other life stages but NOT fetal exposures. Recent studies have demonstrated differential expression and activity of metabolic enzymes such as Cytochrome P450 in fetal versus adult tissue, indicating potential lifestage-dependent variability in metabolic capabilities and greater vulnerability during fetal development not accounted for in current risk assessment practices.[52] This is a critical point to address, as disruptions during fetal development have implications for health and disease in adulthood. EPA should evaluate this rich body of literature to identify the most up-to-date scientific knowledge regarding human variability and susceptibility and incorporate these scientifically-based default values in their assessments unless there are chemical-specific data supporting departing from the defaults. California EPA also developed child-specific risk values for chemicals (e.g., atrazine, lead, nickel, manganese, heptachlor) that specifically address routes of exposure and differences in susceptibility unique to children compared to adults.[53] EPA should review these evaluations and incorporate these values as appropriate. Furthermore, a default guidance principle should be that animal findings are relevant to humans unless there is sufficient and compelling information to support otherwise.

Risk estimates

EPA should not use MOE (margin of exposure) as an analysis method in the risk evaluation process moving forward. MOE is not an estimate of risk—it is a single number that is a version of the "bright line" approach like the Reference Dose (or Reference Concentration for inhalation doses). MOE is calculated by dividing the point of departure (e.g., LOAELs, NOAELs or BMDLs) by estimated exposure values, and this 'bright line' approach does not provide information about the magnitude of the risks above, at, or below this line. Further, it implies that there is a "safe" level of exposure below which no

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[50] California EPA 2009. Cal EPA 2009. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. http://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[51] Cal EPA 2008. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document For the Derivation of Noncancer Reference Exposure Levels[HYPERLINK "http://oehha.ca.gov/media/downloads/crnr/noncancertsdfinal.pdf" \h][HYPERLINK "http://oehha.ca.gov/media/downloads/crnr/noncancertsdfinal.pdf" \h]

[52] Sadler, N.C., Nandhikonda, P., Webb-Robertson, B.J., Ansong, C., Anderson, L.N., Smith, J.N., Corley, R.A. and Wright, A.T., 2016. Hepatic cytochrome P450 activity, abundance, and expression throughout human development. *Drug Metabolism and Disposition*, *44*(7), pp.984-991.

[53] California Environmental Protection Agency. Office of Environmental Health Hazard Assessment (OEHHA). Child-Specific Reference Doses (chRDs) Finalized to Date. Available from: http://oehha.ca.gov/risk-assessment/chrd/table-all-chrds

harm will occur. While this may be true for a select few chemicals, the NAS Science and Decisions report recognizes that this is not a valid assumption for all chemicals and has recommended moving away from such "bright line" approaches which do not establish risk estimates across the full range of exposures.[54] Additionally, the MOE will not provide the necessary information for future analysis of risks and benefits that will be critical for decision-making on these chemicals.[55] We recommend that EPA utilize available analytical methods such as PODs based on a BMD to develop quantified estimates of risk.

EPA appropriately states that a dose-response assessment will be conducted for all identified human health hazard endpoints. PODs should also be developed for every endpoint unless the data are insufficient to develop a model. For calculating cancer or non-cancer risks, we recommend always using a point of departure (POD) of a benchmark dose (BMD) at 1%. The POD should be based on a BMD calculation, not the NOAEL/LOAEL, unless the data are insufficient to model. EPA already recognizes the features that make BMDs superior: BMDs account for the shape of the dose–response function; are independent of study design, such as the space between dosing; and are comparable across chemicals.[56]

Historically, for carcinogens that are direct mutagens or are associated with large human body burdens, EPA has assumed there is no threshold of effect. But the NAS Science and Decisions report highlights the science indicating that this linear presumption with no threshold is appropriate for the calculation of both cancer and non-cancer risks, and regardless of whether a carcinogen is a mutagen. For example, dose-response relationships can be linear at low dose when exposures contribute to an existing disease process, add to background processes and/ or exposures, and interact with interindividual variability or susceptibility.[57] Science and Decisions recommends harmonizing cancer and non-cancer risk assessment approaches. Therefore, for calculating non-mutagen cancer or non-cancer risks based on a POD, EPA should use the same approach as for mutagens, which assumes a straight line from the POD. In fact, a linear relationship may actually underestimate risks for some chemicals where the dose-response curve is supra-linear.

6. Confidential Business Information (CBI) claims should not be used to obscure critical data and information from the public.

Production volumes for both asbestos and pigment violet 29 have been claimed as CBI. Production volume is basic information about a chemical to which the public and scientists should have access. We urge EPA to move forward with substantiating such claims under the new TSCA.

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[54] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009.

[55] McGartland A, Revesz R, Axelrad DA, Dockins C, Sutton P, Woodruff TJ. Estimating the health benefits of environmental regulations. Science (80-). 2017 Aug 4;357(6350):457–8.

[56] Wignall JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, Rusyn I. 2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environmental health perspectives. 122(5).

[57] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. Ch.5